UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,895	02/16/2001	Luiz Belardinelli	MBHB00-081-A	4211

7590 05/07/2003

A. Blair Hughes
McDonnell Boehnen Hulbert & Berghoff
32nd Floor
300 S. Wacker Drive
Chicago, IL 60606

EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/07/2003

5

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,895	BELARDINELLI ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-15 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for design and administration of A_{2B} antagonists to retinal cells in culture and 3-N-propylxanthine to rodents for reducing retinal neovascularization in oxygen induced retinopathy, does not reasonably provide enablement for design and administration of A_{2B} antagonists to any cell in any whole organisms for inhibiting proliferation of any mammalian cell as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the previous Official Action mailed 11/06/01 and 09/10/02.

Applicant's arguments filed 02/21/03 have been fully considered but they are not persuasive.

Applicants argue on page 4 of the response filed 2/21/03 that "[i]n addition to the HREC model, a mouse pup model of oxygen-induced retinopathy has been used to demonstrate the effects of AdoR antagonists on neovascularization. See, Mino et al.... The use of this mouse

model system was described in the specification at page 5, lines 22 through page 6, line 1." Applicants further point out on page 5 that A2B selective antagonists 3-N-propylxanthine (enprofylline) and 3-isobutyl-8-pyrrolikeinoxanthine (IPDX) caused a significant reduction in retinal neovascularization in the mouse pups.

Since the Mino et al. reference is not prior art to the claimed invention, it is only useful for supporting the enablement of the A2B antagonists taught in the specification as filed. The instant specification as filed taught on page 11, that 3'-N-propylxanthine was one of the A2B antagonists tested in the instant invention in HREC cells. Since Mino et al. supports use of this compound in the retina *in vivo* in mice, the Mino et al. reference is considered to enable this compound for the functions taught in Mino et al., the reduction of retinal neovascularization. However, the Mino et al. reference does not correlate to enablement of the breath of instantly claimed methods since instant claim 1 is broadly drawn to inhibition of proliferation of any cell type, and not just retinal cells. As argued previously, the inhibition of retinal cells does not correlate to inhibition of any type of cell *in vivo* as claimed.

Applicants further argue that The Kim and Klotz references are from 1998, three years before the filing of the instant application, and that the specification teaches that at the time of the filing of the application A2B agonists and antagonists were known. As stated above, the Mino et al. reference supports the teaching that 3-N-propylxanthine, used in the instant specification, was sufficient to selectively antagonize the A2B receptor in retinal cells for the function of reducing neovascularization. However, the specification as filed, nor the post art,

does not further support that other A2B specific antagonists (other than the enabled 3-N-propylxanthine) were known that have the claimed functions.

Applicants further state that "[t]he methods by which the antagonists and agonists were or are to be discovered, i.e., by "traditional design methods" is of no importance." However, the instant rejection is maintained because absent further specific guidance for making and using selective A2B antagonists for the functions claimed, one of skill in the art would not be able to make and use the claimed invention for the breath of antagonists other than the 3-N-propylxanthine absent such methods of traditional rational drug design. Thus, the design of new A2B antagonists (other than 3-N-propylxanthine) is pertinent to the instantly claimed invention, since the claims read broadly on *any* A2B antagonist. Applicants have not further addressed the teachings of Lahdenranta et al. and Cao et al. cited in the previous Office action teaching the high level of unpredictability in the art of design of antiangiogenic inhibitors and that there is no known pathogeneisis of neovascularization in ischemic retinopathies and the many variables involved in the development of the retina over time (with dates in the year 2001).

Applicant further states that the specification teaches that one example of an *in vivo* assay is the mouse pup model of oxygen induced retinopathy (page 5, lines 22 through page 6, line 1) which can be used to screen for A2B antagonists and agonists and that Mino et al. demonstrates that such *in vivo* assays do indeed function as disclosed by the specification. However, applicant is widely grouping several different issues together. The instant specification teaches use of HREC (human retinal endothelial cells) for determination of A2B antagonists in a chemotaxis

assay. The mouse pup model is one that is used in hypoxic stimulation of retinopathy. These do not correlate since the HREC cells are not effected by the hypoxia. Furthermore, while one of skill in the art would recognize that it would be possible to take a known A2B antagonist and use it *in vivo* for screening, the reverse is not also true. Screening a compound *in vivo* does not tell the practitioner what the target effected is. Mino et al. for instance took, known antagonists and was investigating their effect on a particular retinopathy. They were not merely testing the retinal cells for the ability to grow or not as a screen for finding an A2B antagonist as instantly claimed. Thus, since the screening is drawn to determination of A2B antagonists, one of skill in the art could readily screen for this in the HREC cells in cell culture, but not first in cells *in vivo*, for the critical determination of the selectively of the antagonist.

Applicant further cited Mino et al. as a reference teaching a ribozyme to A2B receptor *in vivo* to the mouse pup model of oxygen-induced retinopathy. However, these results do not support an enablement of the instant specification as filed, since the instant specification does not provide the teaching of the specific ribozyme used in Mino et al. and thus does not provide that the ribozyme taught in Mino et al. was a part of the applicants invention at the time of filing. The guidance in the instant specification is not supportive at the time the invention was made of making and using antisense and ribozymes to A2B receptor for the reasons argued previously.

Allowable Subject Matter

3. Claims 16-19 are allowable.

4. The closest prior art to claims 16-19, Grant et al. and Grant et al. in view of Kemp et al., Kim et al. and Klotz et al. was overcome by Applicant in filing a declaration according to *In re Katz* showing that the Grant et al. reference was Applicants own work, published less than a year before the priority date of the instant Application. The claims are further free of the prior art since although the art taught the need for A_{2B} specific agonists and antagonists (Kim et al., Klotz et al. and Kemp et al.), the art did not specifically teach the motivation for testing in human retinal endothelial cells as instantly claimed. In regards to claims 1-15, the prior art did not teach nor fairly suggest administration of A_{2B} agonists and antagonists for the functions claimed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 308-3413.

M. M. Schmidt
May 1, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600